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Original Article

The effects of proton pump inhibitor on hepatic vascular responsiveness and hemodynamics in cirrhotic rats

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Abstract

Background: Liver cirrhosis is associated with increased intrahepatic resistance due to hepatic fibrosis and exaggerated vasoconstriction. Recent studies have indicated that proton pump inhibitors (PPIs), in addition to acid suppression, modulate vasoactive substances and vasoresponsiveness. PPIs are frequently prescribed in patients with cirrhosis due to a higher prevalence of peptic ulcers, however other impacts are unknown.

Methods: Liver cirrhosis was induced in Sprague−Dawley rats with common bile duct ligation (BDL). On the 29th day after BDL and after hemodynamic measurements, the intrahepatic vascular responsiveness to high concentrations of endothelin-1 (ET-1) was evaluated after preincubation with (1) Krebs solution (vehicle), (2) esomeprazole (30 μM), or (3) esomeprazole plus N^{ω}-nitro L-arginine (NNA, a non-selective NO synthase (NOS) inhibitor, 10^{-4} M). After perfusion, the hepatic protein expressions of endothelial NOS (eNOS), inducible NOS (iNOS), cyclooxygenase (COX)-1, COX-2, endothelin-1, DDAH-1 (dimethylarginine dimethylaminohydrolase-1, ADMA inhibitor), DDAH-2, ADMA (asymmetrical dimethyl arginine, NOS inhibitor) were evaluated. In the chronic model, the BDL rats received (1) vehicle; or (2) esomeprazole (3.6 mg/kg/day, oral gavage) from the 1st to 28th day after BDL. On the 29th day and after hemodynamic measurements, plasma liver biochemistry and liver fibrosis were evaluated.

Results: Esomeprazole did not affect hepatic ET-1 vasoresponsiveness. The hepatic protein expressions of the aforementioned factors were not significantly different among the groups. There were no significant differences in hemodynamics, liver biochemistry and hepatic fibrosis after chronic esomeprazole administration.

Conclusion: PPIs did not affect hepatic vasoresponsiveness or the release of vasoactive substances. Furthermore, they did not influence hemodynamics, liver biochemistry or severity of hepatic fibrosis in the cirrhotic rats.

Keywords: Endothelin; Liver cirrhosis; Nitric oxide; Portal hypertension; Proton pump inhibitor

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Various kinds of liver damage can lead to fibrogenesis and the formation of regeneration nodules if not controlled appropriately, followed by increased intrahepatic resistance and portal hypertension.[1] In addition to structural changes, increases in vasoconstrictive substances such as endothelin-1 (ET-1) and decreased bioavailability of vasodilatory substances such as nitric oxide (NO) have been shown to play roles in increasing hepatic resistance.[2] Portosystemic collaterals develop to divert stagnant portal blood from a hypertensive portal system, followed by potentially lethal complications. It is widely accepted that modulating intrahepatic resistance is essential to control portal hypertension-related complications.[1]

Proton pump inhibitors (PPIs) exert their potent acid-suppression effect via inhibiting gastric H^+/K^+-ATPase in parietal cells. They are frequently used to treat gastrointestinal disorders that involve the production of gastric acid such as peptic ulcer, gastroesophageal reflux disease (GERD), Barrett's esophagus and *Helicobacter pylori* infection.[3–5] The high oral bioavailability of PPIs and their remarkable efficacy in the sustained suppression of gastric acid secretion mean that they are the most popular type of acid suppressant. In addition, the prevalence of gastric ulcer in cirrhotic patients has been reported to be 20.8%, which is significantly higher than the 4.0% reported in healthy controls.[6] A previous study also reported a higher prevalence of reflux esophagitis in Chinese patients with chronic liver diseases.[7] It is therefore reasonable to assume that the use of PPIs in cirrhotic patients is widespread.

The vascular impact of PPIs beyond acid suppression has recently gained increasing attention. For example, lemiprazole has been shown to inhibit contractile responses in isolated rat aortic rings and relax pre-contracted rat aorta.[8] An experimental inhibitor of H^+/K^+-ATPase (SCH 28080) has also been shown to relax guinea pig and human pulmonary arteries.[9] In addition, a highly specific inhibitor, NC-1300-B, has been shown to cause profound renal vasodilation and inhibit the release of renin.[10] In contrast, PPIs were shown to result in elevated levels of asymmetric dimethylarginine (ADMA) and reduced levels of NO and endothelium-dependent vasodilation in a murine model and ex vivo human tissues. ADMA is an endogenous inhibitor of NO synthase (NOS). PPIs increase levels of ADMA by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), the enzyme that degrades ADMA.[11] Injections of lansoprazole have been shown to increase levels of ADMA in mice by about 20%.[12] Therefore, it would be interesting to investigate whether PPIs influence the levels of NO, DDAH and ADMA in cirrhosis. A recent study suggested that esomeprazole controlled pulmonary inflammation and fibrosis in a murine model of acute lung injury by suppressing the expressions of pro-inflammatory and fibrogenetic molecules.[13] However, whether PPIs affect liver inflammation and fibrosis has yet to be investigated.

Considering the vascular actions of PPIs beyond acid suppression and the frequent prescription of PPIs in cirrhotic patients, this study aimed to investigate hemodynamic changes, intrahepatic vascular responsiveness to ET-1, liver biochemistry and fibrosis in cirrhotic rats exposed to PPIs.

2. Methods

2.1. Animal model

Male Sprague–Dawley rats weighing 240–270 g at the time of surgery were used for the experiments. The rats were housed in plastic cages and allowed free access to food and water. All rats were fasted for 12 h before the operation. Secondary biliary cirrhosis was induced using common bile duct ligation (BDL).[14] Under ketamine anesthesia (100 mg/kg, intramuscularly), the common bile duct was doubly ligated with 3-0 silk. The first ligature was made below the junction of the hepatic ducts and the second ligature was made above the entrance of the pancreatic duct, followed by sectioning the common bile duct between the ligatures. A high yieldof secondary biliary cirrhosis was noted 4 weeks after the ligation.[15] To avoid coagulation defects, the BDL rats received weekly vitamin K injections (50 μg/kg intramuscularly).[16] This study was approved by Taipei Veterans General Hospital Animal Committee (IACUC 2015-109). All animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86-23, revised 1985).

2.2. Measurement of systemic and portal hemodynamics

The right carotid artery was cannulated with a PE-50 catheter that was connected to a Spectramed DTX transducer (Spectramed Inc., Oxnard, CA, USA). Continuous recordings of mean arterial pressure (MAP), heart rate (HR), and portal pressure (PP) were performed on a multi-channel recorder (model RS 3400, Gould Inc., Cupertino, CA, USA). The external zero reference was placed at the level of the midportion of each rat. The abdomen was then opened with a midline incision, and the mesenteric vein was cannulated with a PE-50 catheter connected to a Spectramed DTX transducer. The abdominal cavity was closed and the PP was recorded on the Gould model RS 3400 recorder.[17]

The superior mesenteric artery (SMA) was identified at its aortic origin, and a 5-mm segment was gently dissected free from surrounding tissues. A pulsed-Doppler flow transducer (T206 small animal blood flow meter, Transonic System Inc., Ithaca, NY, USA) was then used to measure SMA flow.[18] Portal flow was also measured using the flow transducer. The measurement point was as proximal to the liver as possible.

Cardiac output (CO) was measured by thermodilution, as previously described.[19] Briefly, a thermistor was placed in the aortic arch just distal to the aortic valve and a thermal indicator (100 μL of normal saline) was injected into the right

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